Pharmacologic compound to mitigate presbyopia symptoms

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Research Article

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Abstract

Purpose

To assess the effect of a compound of low dose Pilocarpine, Brimonidine and Oxymetazoline (PBO) in a group of presbyopic individuals.

Materials and Methods

We recruited a group of 11 presbyopic individuals from June to July 2020. The PBO compound was instilled in the non-dominant eye and low Pilocarpine or Brimonidine alone were instilled in the other eye. Under corrected near visual acuity using the Jaeger notation, under corrected and corrected distance visual acuity, intraocular pressure, pupil diameter, and lines gained were recorded before and one hour after instillation of the drops.

Results

One hour after drops binocular Jaeger was 2.45 +/ 1.36 SD range (1 – 4) ($p \leq 0.003$) PBO in the non-dominant eye Jaeger was 2.09 +/- 1.446 SD range (1 – 5) ($p \leq 0.0001$) Jaeger in the dominant eye with Pilocarpine or Brimonidine 3.82 +/-1.601 SD range (1 – 6) ($p \leq 0.032$). Jaeger in eyes instilled with Pilocarpine 4.20 +/-1.483 SD range (2 – 6) ($p \leq 0.102$). Jaeger in eyes instilled with Brimonidine 3.50 +/-1.761 range (1 – 5) ($p \leq 0.250$). Lines gained PBO non dominant eye 3.73 +/-1.42 SD range (2 – 6) Lines gained in the dominant eye with Pilocarpine or Brimonidine 2 +/-1.89 SD range (0 – 6). Lines gained in eyes with Pilocarpine 1.60 +/-0.89 SD range (1 – 3). Lines gained in eyes with Brimonidine 2.33 +/- 2.50 SD range (0 – 6).

Discussion

Low dose Pilocarpine, Brimonidine, Oxymetazoline compound showed effectiveness improving near distance vision one hour after instillation compared to low dose Pilocarpine and Brimonidine alone in a group of 11 presbyopic individuals.

Summary

A novel pharmacological compound of pilocarpine, brimonidine and oxymetazoline has a synergistic effect improving near uncorrected visual acuity compared to pilocarpine and brimonidine alone.

Introduction

Presbyopia is known, for the refractive surgeon, as the ultimate goal for vision correction. It entitles a mayor challenge due to the complex mechanism the eye has to achieve accommodation, involving the pupil, the lens and the ciliary body contraction. Attempts for correction include: refraction: monovision with contact lens, [1] laser surgery monovision, multifocal cornea, [2–4] micro monovision, [5] Inlays: Kamra, [6] Raindrop (now discontinued), [7] Scleral expansion implants, [8] and lens related: Femtosecond laser, [9] Pseudo accommodative lens: Cristalens, [10] multifocal intraocular lenses. [11]

Pilocarpine is a parasymphatetic mimetic drug binding to muscarinic receptors m3. It is mainly used for the treatment of narrow angle glaucoma in concentrations ranging from 1–4% for more than one hundred years. Causing miosis, ciliary body contraction, pulling the scleral spur, then lowering intraocular pressure. [12]Among the side effects are ciliary spasm, myopization, red eye, eye brow pain, and posterior iris synechiae on chronic use. [13, 14] Brimonidine is an Alpha 2 adrenergic agonist use for the treatment of glaucoma on concentrations from 0.15 to 0.2%. [15,16] It blocks the alpha 2 receptors of the iris dilator muscle, inhibiting its function, and then inducing miosis. This side effect has been used to control nocturnal glare and halos experimented by patients after laser excimer procedures. [17–19] Oxymetazoline is an alfa 1 and partial alfa 2 adrenergic agonist used as vasoconstrictor for the treatment of red eye, and has an effect dilating the pupil due to it prejunctional alfa 2 activity leading to a reduction of sensory neurotransmitter release, as evident from a decrease in evoked sphincter contraction.

We prepared a compound using Pilocarpine, Brimonidine and Oxymetazoline in low doses and compared it with low dose Pilocarpine and low dose Brimonidine alone to determine its effect of near vision, intraocular pressure and pupil diameter in order to ammeliorate presbyopia symptoms and secondary effects related to drug use such as pain and blurry vision. [20,21]

Material And Methods

A prospective clinical trial was conducted from June to July 2020 we selected patients presenting at Optall Vision eye center in México City with presbyopia symptoms. The study was approved by the ethics committee of Optall Vision Eye Center in México City in accordance with the ethical standards of the 1964 Declaration of Helsikinki and. All patients signed and informed consent to participate in the study. We included healthy patients with presbyopia, corrected visual acuity 20/25 or better. Presbyopia diagnosis was determined if uncorrected near vision acuity was equal of less than Jaeger 3 in the Rosenbaum chart improving at least Jaeger 2 with the use of at least a +1.00 D lens. We registered age, gender, ocular dominance, uncorrected visual acuity (UCVA), best corrected visual acuity (BCVA), uncorrected near vision acuity with the Rosenbaum Jaeger chart, (UNVA), best corrected near vision acuity (BCNVA) Intraocular pressure with Goldmann applanation tonometer (IOP) Pupil diameter in photopic and scotopic conditions (PD), Biomicroscopic slit lamp exam, eye fundus exam. A compound of low dose Pilocarpine (0.24%) (Pil, Sophia Laboratories, México), Brimonidine (0.052%) (Alphagan P, Allergan Laboratories, Irvine CA) Oxymetazoline/Sodium Hyaluronate (0.83 mg/0.10mg) (Hyalox, Laboratorios Sophia, México) (PBO) was prepared. Also, a dilution of Pilocarpine (0.24%) (Pil, Sophia

Laboratories, México) with Saline Solution 0.9% (Solución CS. Pisa Laboratories, México) and a dilution of Brimonidine (0.052%) (Agglad, Sophia Laboratories, México) with Saline Solution 0.9% (Solución CS. Pisa Laboratories, México) was prepared. One drop of PBO compound was instilled in the non-dominant eye and one drop of Pilocarpine or Brimonidine dilution were instilled alternatively in the dominant eye of consecutive patients. After one-hour uncorrected visual acuity (UCVA), best corrected visual acuity (BCVA), uncorrected near vision acuity (UNVA), best corrected near vision acuity (BCNVA) Intraocular pressure (IOP) Pupil diameter (PD) Pain in an Analogue Visual Scale (AVS) was measured 0 – 10. Hyperemia was measured from 0 to 4. Statistical analysis was run with SPSS statistica using the Pearson and Spearman correlation analysis and Wilcoxon non parametric test. P value is significant when is equal or less than 0.05.

Results

Descriptive statistics. 11 patients were recruited to participate in the study, 7 male and 4 female. Dominant eye was right in 6 patients and left in 5 patients. Average age was 49.27 +/- 1.84 SD range (44 – 56 years). BCVA was 20/20 in all eyes. Jaeger was measured binocular and individually for each eye. Binocular Jaeger score was 5.82 +/-1.04 SD range (3 – 7). Jaeger score right eye was 5.91 +/-1.514 SD range (3 – 8). Jaeger score left eye was 5.64 +/-1.502 SD range (3 – 7). Intraocular pressure OD was 13 mmHg +/- 2.145 SD range (10 – 16 mmHg). Intraocular pressure OS was 13 mmHg +/-2.145 SD range (10 – 16 mmHg). Photopic pupilar diameter OD was 3.73 mm +/- 0.46 SD range (3 – 4 mm). Photopic pupilar diameter OS was 3.73 mm +/- 0.46 SD range (3 – 4 mm). Scotopic pupilar diameter OD was 4.63 mm +/- 0.636 SD range (3.5 – 5 mm). Scotopic pupilar diameter OS was 4.63 mm +/- 0.636 SD range (3.5 – 5 mm). BPO compound was instilled in the non-dominant eye of all participants. Pilocarpine and Brimonidine dilutions were alternatively instilled in the dominant eye of all participants. One hour after drops instillation binocular Jaeger was 2.45 +/ 1.36 SD range (1 – 4) ($p \leq 0.003$) PBO in the non-dominant eye Jaeger was 2.09 +/- 1.446 SD range (1 – 5) ($p \leq 0.0001$) Jaeger in the dominant eye with Pilocarpine or Brimonidine 3.82 +/-1.601 SD range (1 – 6) ($p \leq 0.032$). Jaeger in eyes instilled with Pilocarpine 4.20 +/-1.483 SD range (2 – 6) ($p \leq 0.102$). Jaeger in eyes instilled with Brimonidine 3.50 +/-1.761 range (1 – 5) ($p \leq 0.250$). Lines gained PBO non dominant eye 3.73 +/-1.42 SD range (2 – 6) Lines gained in the dominant eye with Pilocarpine or Brimonidine 2 +/-1.89 SD range (0 – 6). Lines gained in eyes with Pilocarpine 1.60 +/-0.89 SD range (1 – 3). Lines gained in eyes with Brimonidine 2.33 +/- 2.50 SD range (0 – 6). Intraocular pressure OD was 13 mmHg +/- 2.145 SD range (10-16). Intraocular pressure OS was 13 mmHg +/- 2.145 SD range (10-16). Photopic pupilar diameter PBO non dominant eye was 2.63 mm +/-0.63 SD range (2 – 4) ($p \leq 0.039$). Photopic pupilar diameter Pilocarpine or Brimonidine dominant eye was 3.13 mm +/-0.63 SD range (2 – 4) ($p \leq 0.059$). Scotopic pupilar diameter PBO non dominant eye was 2.68 mm +/- 0.60 SD range (2 – 4) ($p \leq 0.042$). Scotopic pupilar diameter Pilocarpine, Brimonidine dominant eye was 2.90 mm +/-0.66 SD range (2 – 4) ($p \leq 0.061$). Pain in the PBO non dominant eye was in AVS 0. Pain in the Pilocarpine or Brimonidine dominant eye in a AVS was reported by 2 patients grade 2 and 3 respectively. Hyperemia in the PBO non dominant eye was 1 in 1 eye of 11 (9%). Hyperemia in the Pilocarpine Brimonidine dominant eye was present in 4 patients: 3 with grade 1

hyperemia and 1 with grade 2 hyperemia (36%). BCVA remained 20/20 in all patients, intraocular pressure remained unchanged in both groups. No patient reported blurry vision at distance or headache.

Discussion

There are several efforts to mitigate presbyopia symptoms using drugs targeting the iris sphincter and the dilator in presbyopic individuals. In 1990 Rosenfeld documented the use of phenylephrine and thymoxamine (an alpha antagonist) achieving 1.5 D accommodative amplitude lasting only two hours. [22] Benozzi reported a combination of Pilocarpine 1–2% combined with Diclofenac to treat presbyopic individuals for a 5 years period. At such dose 20% of patients experienced eye burning, and ocular discomfort right after drop instillation. 1% discontinued treatment due to intolerance to medication, 4% preferred glasses. [23]

Brimonidine has a direct effect in pupil size after instillation. It has a miotic effect under photopic and scotopic conditions. [24] It has been used by refractive surgeons in the commercial presentations 0.2% and 0.15% to successfully palliate adverse effect of laser procedures such as glare and halos, obtaining the effect 30 minutes after instillation and lasting up to six hours. [25–26]

The use of Brimonidine in a lower dose (0.1%) has shown a similar effect on pupil size than the regular concentrations. [27] Base line photopic pupil diameter was 3.73 mm +/- 0.46 range (3 to 4). One hour after PBO instillation in the non-dominant eye, pupil diameter was 2.63 mm +/-0.63 range (2 to 4) ($p \leq 0.039$). In the Pilocarpine or Brimonidine group pupilar diameter was 3.13 mm +/-0.63 range (2 to 4) ($p \leq 0.059$). Baseline scotopic pupil diameter was 4.63 mm +/-0.63 range (3.5 to 5). One hour after PBO instillation the pupil diameter was 2.68 mm +/- 0.60 range (2 to 4) ($p \leq 0.042$). In the Pilocarpine or Brimonidine group, pupilar diameter was 2.9 mm +/- 0.66 range (2 to 4) ($p \leq 0.061$) (Table 3). We researched the effect of low dose of Pilocarpine, Brimonidine and Oxymetazoline (PBO) mitigating the effects of presbyopia in eleven healthy individuals in order to avoid undesirable effects as pain, burning, discomfort and blurry distance vision. One hour after instillation of the compound in the non-dominant eye, Jaeger notation improved from 5.82 to 2.09 ($p \leq 0.0001$) compared to low dose Pilocarpine 4.2 ($p \leq 0.102$) and non-dominant low dose Brimonidine 3.5 ($p \leq 0.25$) alone (Table 1). The combination showed a significant improvement in the Jaeger notation one hour after instillation compared to Pilocarpine and Brimonidine alone.

Renna published in 2016 a compound including Pilocarpine 0.247%, Phenylephrine 0.78%, Polyethylene glycol 0.09%, Nepafenac 0.023%, Pheniramine 0.034% and Naphazoline 0.003% instilled binocularly in 14 presbyopic subjects. [28] The results showed 2 to 3 lines of UNVA improvement. No patient had lost of UDVA in each eye and binocularly. Our study showed 2 to 6 lines of UNVA improvement. Average 3.73 lines compared to 1.6 with low dose Pilocarpine and 2.33 with low dose Brimonidine. Accordingly, no patients lost UDVA (Table 2). In 2018 Vargas, from the same study group published a series of 117 presbyopic patients using the same formulation achieving significant improving of UNVA in 92.3% of patients 2 hours post eye drop instillation. 14 patients reported headache, 1 patient was intolerant to the

preparation. [29] Giovanna Benozzi reports in 2020 a retrospective series from 1 up to 8 years follow up of 910 patients, with high adherence to treatment and discontinuing the use of presbyopia spectacles. The most frequent side effect was dim vision 246 individuals (26%), headache 119 (12.9%), ocular surface burning 86 (9.3%). [30] Although is a small population, no patient reported headache in our series. Pain in the PBO non dominant eye was in AVS 0. Pain in the Pilocarpine or Brimonidine dominant eye in an AVS was reported by 2 patients grade 2 and 3 respectively. Hyperemia in the PBO non dominant eye was 1 in 1 eye of 11 (9%). Hyperemia in the Pilocarpine Brimonidine dominant eye was present in 4 patients: 3 with grade 1 hyperemia and 1 with grade 2 hyperemia (36%).

The combination of low dose Pilocarpine, a muscarinic parasympathomimetic, acting on receptors at the iris sphincter and the ciliary muscle, with Brimonidine and Oxymetazoline at low doses has an additive effect one hour after instillation. Brimonidine acts at the alpha 2 receptor of the iris dilator muscle, inhibiting its function and inducing indirect miosis. Combining those agents to induce miosis gave us the rationale to lower the concentration to achieve a similar result and avoiding the side effects such as pain and discomfort. We believe that lowering the Pilocarpine dose avoids ciliary muscle spasm related pain and induced myopia, affecting distance vision. None of our patients reported blurry vision at distance. No patient loss lines of UDVA. Oxymetazoline and alpha 1 and partial alpha 2 imidazolic agonist has a mydriatic effect. We believe it opposes the action of the Pilocarpine and Brimonidine, hence avoiding spasm of the iris sphincter, and allowing pupil movement. [31]

This novel combination of Pilocarpine, Brimonidine and Oxymetazoline in low doses has an synergistic effect improving near vision in presbyopic patients, achieving at least up to 3.73 lines of near vision gain on the Jaeger notation. This compound has a potential use to mitigate the symptoms of presbyopia in healthy individuals. Further studies are being designed to document the long term effect of this compound in patients with presbyopia.

Conclusion

The combination of three drugs in low doses: one parasimpathetic mimetic (Pilocarpine) and two alpha adrenergics (Brimonidine (2) and Oxymetazoline (1) has shown a significative synergistic effect improving near vision as measured with the Rosembaum chart with Jaeger notation one hour after instilation in the non-dominant eye of healthy presbyopic patients compared to Pilocarpine and Brimonidine alone in low doses.

Table 1
Uncorrected near visual acuity improvement one hour after instilling drops

Drug	Jaeger	SD	range	p
Baseline	5.82	1.04		
1 hr after	2.45	1.36	1 to 4	0.003
PBO	2.09	1.44	1 to 5	0.0001
Pil or Brim	3.82	1.6	1 to 6	0.032
Pil	4.2	1.48	2 to 6	0.102
Brimonidine	3.5	1.76	1 to 5	0.25

PBO Pilocarpine, Brimonidine, Oxymetazoline

Pil Pilocarpine

Brim Brimonidine

SD Standard Deviation

Table 2
Lines gained of uncorrected near visual acuity one hour after instilling drops

Drug	Lines gained	SD	range
PBO	3.73	1.42	2 to 6
Pil or Brim	2	1.89	0 to 6
Pilocarpine	1.6	0.89	1 to 3
Brimonidine	2.33	2.5	0 to 6

PBO Pilocarpine, Brimonidine, Oxymetazoline

Pil Pilocarpine

Brim Brimonidine

SD Standard Deviation

Table 3
Photopic and Scotopic pupil diameter one hour after instilling drops

Drug	Photopic PD	SD	range	p
Baseline	3.73	0.46	3 to 4	
PBO	2.63	0.63	2. to 4	0.039
Pil or Brim	2.9	0.63	2 to 4	0.059
	Scotopic PD			
Baseline	4.63	0.63	3.5 to 5	
PBO	2.68	2.6	2 to 4	0.042
Pil or Brim	3.13	0.66	2 to 4	0.061

PBO Pilocarpine, Brimonidine, Oxymetazoline

Pil Pilocarpine

Brim Brimonidine

PD Pupil Diameter

SD Standard Deviation

References

1. - Morgan PB, Efron N (2009) Contact lens correction of presbyopia. Cont Lens Anterior Eye 32(4):191–192
2. - Stival LR, Figueiredo MN, Santhiago MR (2018) Presbyopic Excimer Laser Ablation: A Review. J Refract Surg 34(10):698–710
3. - Alió JL, Amparo F, Ortiz D, Moreno L (2009) Corneal multifocality with excimer laser for presbyopia correction. Curr Opin Ophthalmol 20(4):264–271
4. - Pallikaris IG, Panagopoulou SI (2015) PresbyLASIK approach for the correction of presbyopia. Curr Opin Ophthalmol 26(4):265–272
5. - Reinstein DZ, Carp GI, Archer TJ, Gobbe M (2012) LASIK for presbyopia correction in emmetropic patients using aspheric ablation profiles and a micro-monovision protocol with the Carl Zeiss Meditec MEL 80 and VisuMax. J Refract Surg 28(8):531–541
6. - Naroo SA, Bilkhu PS (2016) Clinical utility of the KAMRA corneal inlay. Clin Ophthalmol 10:913–919. Published 2016 May 18

7. - Moshirfar M, Desautels JD, Wallace RT, Koen N, Hoopes PC (2017) Comparison of FDA safety and efficacy data for KAMRA and Raindrop corneal inlays. Int J Ophthalmol 10(9):1446–1451. Published 2017 Sep 18
8. - Malecaze FJ, Gazagne CS, Tarroux MC, Gorrand JM (2001) Scleral expansion bands for presbyopia. Ophthalmology 108(12):2165–2171. doi:10.1016/s0161-6420(01)00591-7
9. - Žiak P, Lucká K, Mojžiš P, Katuščáková I, Halička J (2016) Prvé skúsenosti s korekciou presbyopie femtosekundovým laserom metódou INTRACOR [First Experience with Femtosecond Laser Presbyopia Correction Method INTRACOR]. Cesk Slov Oftalmol 72(3):51–57
10. - Cumming JS (2006) Performance of the crystalens. J Refract Surg 22(7):633–635
11. - Carson D, Hill WE, Hong X, Karakelle M (2014) Optical bench performance of AcrySof(®) IQ ReSTOR(®), AT LISA(®) tri, and FineVision(®) intraocular lenses. Clin Ophthalmol 8:2105–2113
12. - Poinoosawmy D, Nagasubramanian S, Brown NA (1976) Effect of pilocarpine on visual acuity and on the dimensions of the cornea and anterior chamber. Br J Ophthalmol 60(10):676–679
13. - Place VA, Fisher M, Herbst S, Gordon L, Merrill R (1975) Comparative pharmacologic effects of pilocarpine administered to normal subjects by eyedrops or by ocular therapeutic systems. Am J Ophthalmol 80(4):706–712
14. - Smith SE, Smith SA, Friedmann AI, Chaston JM (1979) Comparison of the pupillary, refractive, and hypotensive effects of Ocusert-40 and pilocarpine eyedrops in the treatment of chronic simple glaucoma. Br J Ophthalmol 63(4):228–232
15. - Bacskulin A, Kundt G, Guthoff R. Efficiency of pupillary stretching in cataract surgery. Eur J Ophthalmol. 1998;8(4):230-233. Carstocea B, Gafencu O, Armegioiu M et al. Dificultaţi în chirurgia cristalinului la bolnavul vechi glaucomatos [Difficulties in cataract surgery of patient with old glaucoma]. Oftalmologia. 2001;54(4):36-39
16. - Rahman MQ, Ramaesh K, Montgomery DM (2010) Brimonidine for glaucoma. Expert Opin Drug Saf 9(3):483–491
17. - Mundorf T, Williams R, Whitcup S, Felix C, Batoosingh A (2004 Aug;20(4):372]) A 3-month comparison of efficacy and safety of brimonidine-purite 0.15% and brimonidine 0.2% in patients with glaucoma or ocular hypertension [published correction appears in J Ocul Pharmacol Ther. J Ocul Pharmacol Ther. 2003;19(1):37-44
18. - Besada E, Reed K, Najman P, Shechtman D, Hardigan P (2011) Pupillometry study of brimonidine tartrate 0.2% and apraclonidine 0.5%. J Clin Pharmacol 51(12):1690–1695
19. - Kesler A, Shemesh G, Rothkoff L, Lazar M (2004) Effect of brimonidine tartrate 0.2% ophthalmic solution on pupil size. J Cataract Refract Surg 30(8):1707–1710
20. - Lee JH, You YS, Choe CM, Lee ES (2008) Efficacy of brimonidine tartrate 0.2% ophthalmic solution in reducing halos after laser in situ keratomileusis. J Cataract Refract Surg 34(6):963–967
21. - Fuder H (1994) Functional consequences of prejunctional receptor activation or blockade in the iris. J Ocul Pharmacol 10(1):109–123

22. - Rosenfield M (1990) The influence of Alpha-adrenergic-agents on tonic accommodation. Curr Eye Res 9(3):267–272
23. - Jorge Benozzi Presbyopia: a New Potential Pharmacological Treatment MEHDI Ophthalmology Journal 2012; Vol. 1, No 1
24. - McDonald JE 2nd, El-Moatassem Kotb AM, Decker BB.J Cataract Refract Surg. 2001 Apr;27(4):560–4
25. - Lee JH, You YS, Choe CM, Lee ES (2008) Efficacy of brimonidine tartrate 0.2% ophthalmic solution in reducing halos after laser in situ keratomileusis. J Cataract Refract Surg 34(6):963–967
26. - Edwards JD, Burka JM, Bower KS, Stutzman RD, Sediq DA, Rabin JC (2008) Effect of brimonidine tartrate 0.15% on night-vision difficulty and contrast testing after refractive surgery. J Cataract Refract Surg 34(9):1538–1541
27. - Kato COS, Shimizu K, Kamiya K, Ishikawa H, Igarashi A. Effects of brimonidine tartrate 0.1% ophthalmic solution on the pupil, refraction, and light reflex. Sci Rep. 2018;8(1):9003. Published 2018 Jun 13. doi:10.1038/s41598-018-27436-8
28. - Renna A, Vejarano LF, De la Cruz E, Alió JL (2016) Pharmacological treatment of presbyopia by novel binocularly instilled eye drops: a pilot study. Ophthalmol Ther 5(1):63–73
29. - Vargas V, Vejarano F, Alió JL (2019) Near Vision Improvement with the Use of a New Topical Compound for Presbyopia Correction: A Prospective, Consecutive Interventional Non-Comparative Clinical Study. Ophthalmol Ther 8(1):31–39. doi:10.1007/s40123-018-0154-6
30. - Benozzi G, Perez C, Leiro J, Facal S, Orman B (2020) Presbyopia Treatment With Eye Drops: An Eight Year Retrospective Study. Transl Vis Sci Technol 9(7):25. doi:10.1167/tvst.9.7.25 Published 2020 Jun 23.
31. - Chu TC, Ogidigben MJ, Potter DE (1996) Oxymetazoline: potential mechanisms of inhibitory effects on aqueous humor dynamics. Pharmacology 53(4):259–270. doi:10.1159/000139438